Inhibition by Morphine of Repetitive Activation of Cat Spinal Motoneurones

INAUGURALDISSERTATION

zur Erlangung der Doktorwürde der

HOHEN MEDIZINISCHEN FAKULTÄT
DER UNIVERSITÄT DES SAARLANDES

vorgelegt von

Dr. Werner Grossmann

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Aus dem Institut für Pharmakologie und Toxikologie
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Direktor: Professor Dr. med. Walter RUMMEL

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INTRODUCTION

Morphine has been reported by numerous investigators to depress polysynaptic reflex activity in spinal animals (BLUME, 1927; WIKLER, 1944, 1945; HOUDE et al., 1951 a,b; IRVIN et al., 1951; COOK and BONNYCASTLE, 1953; ANGELUCCI, 1956; MARTIN et al., 1964), whereas monosynaptic reflexes were not found to be influenced uniformly. It has, therefore, been suggested that morphine acts primarily on interneurones.

Since, however, morphine has been shown to depress responses elicited by repetitive stimulation in monosynaptic pathways (JURNA and SCHÄFER, 1965; JURNA, 1966), it might be assumed that the target of the drug is not the interneurone but a process which develops during repetitive activation. The aim of the present study has been to further investigate this problem by assessing the effect of morphine on single spinal neurones.

METHODS

1. General procedure. The experiments were performed on 12 cats weighing from 2.5 to 3.8 kg. The operation was carried out under halothane anesthesia. The animals were intercollicularly decerebrated and spinalized at the lower thoracic level. The spinal cord was exposed from the lower lumbar to the upper sacral region and the

ventral roots L_7 and S_1 were prepared for stimulation. After immobilization with gallamine, artificial respiration was employed and the thorax opened on both sides.

Body temperature was monitored in the rectum and in the pool of paraffin oil covering the spinal cord and kept between 36.5° and 38°C. One cannula was inserted into one of the carotid arteries for blood pressure recording, and another into one of the femoral veins for intravenous injections. A plasma expander (polyvinylpyrrolidone) was infused whenever necessary. Experiments in which the blood pressure dropped below 70 mm Hg and remained there for more than 10 min were discarded. In general, the blood pressure values ranged from 120 to 180 mm Hg, and morphine in the dose applied reduced it by about 30 mm Hg maximally for about 5 - 10 min.

2. Stimulation and recording. The results presented in this paper are based on the recordings obtained from 35 neurones (22 motoneurones and 13 interneurones) under the influence of morphine or the morphine antagonist levallorphan.

Intracellular recording was carried out with glass micropipettes filled with 2 M K-citrate solution. The DC electrode resistance ranged from 10 to 16 MΩ. Recording of the potentials was performed with a feed-

back amplifier in a cathode-follower configuration with an amplification factor of 1.

Motoneurones were activated antidromically and orthodromically by stimulation of the cut ventral or dorsal roots L_7 or S_1. Temporal facilitation of monosynaptic excitatory postsynaptic potentials (EPSPs) was elicited by trains of pulses applied to the medial or lateral gastrocnemius nerves, and inhibitory postsynaptic potentials (IPSPs) were produced in gastrocnemius-soleus motoneurones by stimulation of the sural nerve; in these experiments, the dorsal roots L_7 and S_1 were left unsevered. Interneurones were activated by stimulation of the dorsal roots L_7 or S_1 and their potentials recorded either intra- or extracellularly.

Changes in the excitability of the terminals of primary afferents from muscle spindles or the skin were determined according to the method described by WALL (1958). Tungsten carbide electrodes (Duraprobe; tip diameter 5 µ; electrode resistance 10 - 15 MΩ), insulated apart from 5 µ of the tip were positioned within the nucleus of the gastrocnemius-soleus motoneurones or in the dorsal horn to apply the stimulus. The interval between the conditioning stimulation of the peripheral nerves and the test stimulus was continuously changed, and the responses to the test stimulus with and without conditioning were recorded alternately. The antidromic volley set up by the test stimulus was not integrated,

as has been done by WALL (1958), but only the amplitude of the response was measured.

Single rectangular pulses of 0.05 msec duration were delivered for stimulation to the roots or nerves with pairs of platinum wire electrodes. The stimulation frequency was 1 pulse/sec, except for the experiments in which temporal facilitation of monosynaptic EPSPs or excitability changes of primary afferent terminals were elicited with trains of pulses of a frequency of 200 - 500 pulses/sec (train duration: 10 - 40 msec; repetition rate: 0.4 trains/sec.).

3. Drugs. The drugs used were halothane (Fluothane^{R}, Rhein-Pharma, Heidelberg), gallamine triethyl iodide (Flaxedil^{R}, Abbot, Ingelheim/Rhein), morphine hydrochloride (Merck, Darmstadt) and levallorphan (Lorfan^{R}, Hoffmann-La Roche, Grenzach/Baden).

RESULTS

1. Antidromic and orthodromic activation of motoneurones.

The effect of morphine 2 mg/kg on the action potentials evoked by antidromic or orthodromic stimulation was studied in 15 motoneurones. The action potentials generated by stimulation of the

ventral roots L_7 and S_1 were changed neither in their amplitude, which ranged from 60 to 80 mV, and their duration, nor in their rates of rise and fall, which were about 260 mV/sec and 120 mV/sec respectively. Monosynaptic activation of motoneurones was generally not influenced by morphine, whereas polysynaptic activation was markedly depressed or even abolished.

Fig. 1 A presents recordings obtained from a motoneurone activated by stimulation of the ventral root L_7. Stimulation of the corresponding dorsal root produced a monosynaptic excitatory postsynaptic potential (EPSPs) which generated an action potential and was followed by polysynaptic EPSPs. Five minutes after the injection of morphine, the action potentials produced by antidromic and by monosynaptic activation. were unchanged. The amplitude of the polysynaptic EPSPs, however, was reduced.

Depression by morphine of polysynaptic EPSPs could eventually inhibit a motoneurone to generate action potentials to polysynaptic activation. This is exemplified by Fig. 1 B, where mono- and polysynaptic EPSPs evoked action potentials before the administration of morphine. After morphine the probability that action potentials were generated by polysynaptic EPSPs was much reduced. Mostly, monosynaptic EPSPs were not diminished by morphine, but sometimes, as in this case, a reduction of the amplitude was found, although the resting

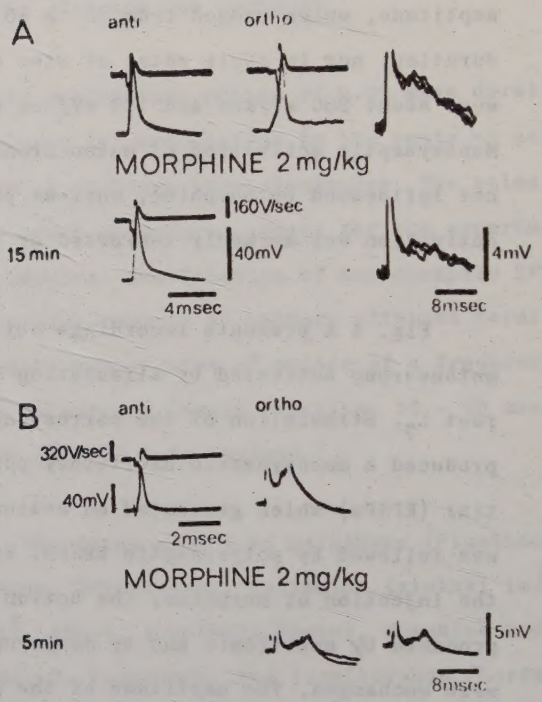


Fig. 1

Effect of morphine on anti- and orthodromic activation of two wpinal motoneurones (A and B). First column of recordings: responses evoked by stimulation of the ventral root L_7 (anti). Lower tracings: conventional recording of action potentials. Upper tracings: electrical differentiation of the action potentials. Second and third column of recordings: responses evoked by stimulation of the dorsal roo L_7 with single pulses (ortho). In A the recordings in the third column were taken at higher amplification than the one in the second column. In B all orthodromic responses were recorded at high amplification.

potential had remained stable at a value of 50 mV.

The morphine antagonist levallorphan effectively antagonized the action of morphine on polysynaptic EPSPs. Fig. 2 shows recordings from a motoneurone which was penetrated by the microelectrode 18 min after an administration of morphine. There were nearly no signs of polysynaptic excitation. Twenty min after the injection of levallorphan 0.2 mg/kg polysynaptic EPSPs of a rather high amplitude had developed which made the cell fire repeatedly. An additional injection of morphine 2 mg/kg reduced the polysynaptic EPSPs and inhibited the generation of repetitive action potentials. The action potentials elicited by antidromic stimulation and the monosynaptic EPSPs were not influenced by the drugs.

2. Inhibition from cutaneous afferents.

The polysynaptic EPSPs described in the preceding part of this paper were elicited by stimulation of dorsal roots which contain afferents mediating not only excitatory but also inhibitory influences on motoneurones. Therefore, the depression of polysynaptic EPSPs produced by morphine might have resulted from an increase of inhibitory postsynaptic potentials (IPSPs). KRUGLOV (1964) described that morphine in rather high doses (5 - 10 mg/kg) enhances the inhibition exerted by a disynaptic pathway on monosynaptic mass reflexes (direct inhibition), whereas the inhibition brought

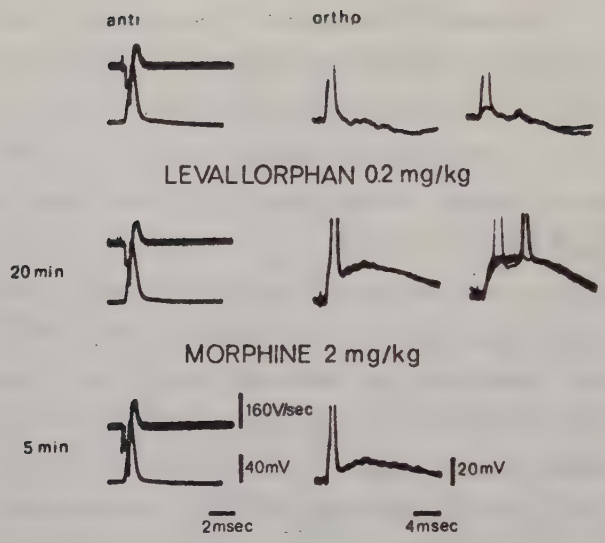


Fig. 2

Effect of levallorphan and morphine on anti- and orthodromic activation of a spinal motoneurone. Stimulation of ventral and dorsal roots S_1 with single pulses. Recordings as in Fig. 1. The motoneurone was penetrated by the microelectrode 18 min after an injection of morphine.

about by way of polysynaptic pathways was rather diminished. SATOH and TAKAGI (1971) found that morphine in a low dose (5 mg/kg) facilitated postsynaptic inhibition of monosynaptic reflexes in decerebrate, but not in spinal cats; a high dose (10 mg/kg) increased postsynaptic inhibition also in spinalized cats. Other authors, however, reported that direct inhibition was not affected by morphine (PINTO CORRADO and LONGO, 1961), or that the alkaloid initially increased direct inhibition and later on diminished it (CURTIS and DUGGAN, 1969). Recurrent inhibition was found to be reduced by morphine (KRUGLOV, 1964; CURTIS and DUGGAN, 1969; FELPEL et al., 1969).

Since morphine in the dose employed in these experiments might have reduced polysynaptic excitation of motoneurones by enhancing inhibition, experiments were performed on 8 gastrocnemius-soleus motoneurones, in which IPSPs were elicited by stimulation of the sural nerve.

In 2 motoneurones, the IPSPs were diminished by morphine. Recordings obtained from one of them are shown in Fig. 3. It should be noticed that in this cell the resting potential increased by 4 mV about 8 min after the injection of morphine and remained subsequently at that level. This increase may account for the change in the amplitude and after-hyperpolarization of the action potential at 10 min (Fig. 3;

10 min after morphine). Following the recordings at 10 min after morphine, levallorphan was injected and increased the amplitude of the IPSPs (Fig. 3; 7 min after levallorphan).

One of the 8 gastrocnemius-soleus motoneurones was penetrated by the micropipette 12 min after the administration of morphine and the IPSPs to sural nerve stimulation were recorded. Subsequent injection of levallorphan 0.2 mg/kg increased the amplitude of the IPSPs. This might indicate that the inhibition had been reduced by the preceding injection of morphine.

In 5 of the 8 motoneurones the IPSPs remained unchanged after morphine 2 mg/kg. This is illustrated by the recordings of Fig. 4 which have been obtained from a motoneurone that was kept impaled at a stable resting potential of 52 mV for more that 20 min after the injection of morphine. Repeated injections of morphine 2 mg/kg or an administration of levallorphan 0.2 mg/kg produced no distinct changes in the IPSPs of these neurones.

It thus seems justified to assume that the depression of polysynaptic EPSPs is not due to an increase of IPSPs and, moreover, that polysynaptic EPSPs are much more sensitive to morphine than are IPSPs.

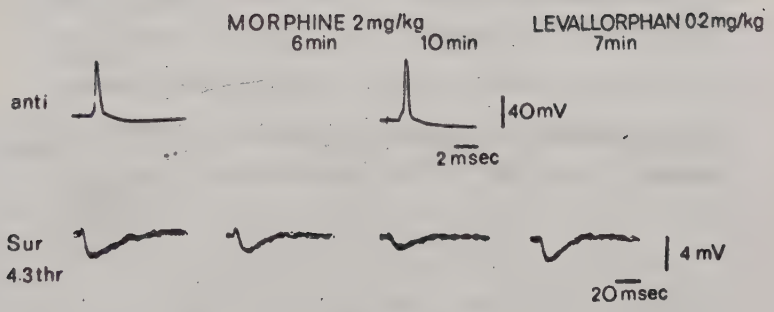


Fig. 3

Effect of morphine and levallorphan on IPSPs elicited in a lateral gastrocnemius motoneurone by stimulation of the sural nerve with single pulses. Upper row of recordings: action potentials elicited by stimulation of the ventral root L_7 (anti). Lower row of recordings: IPSPs produced by sural nerve stimulation with a strength 4.3 times threshold (Sur).

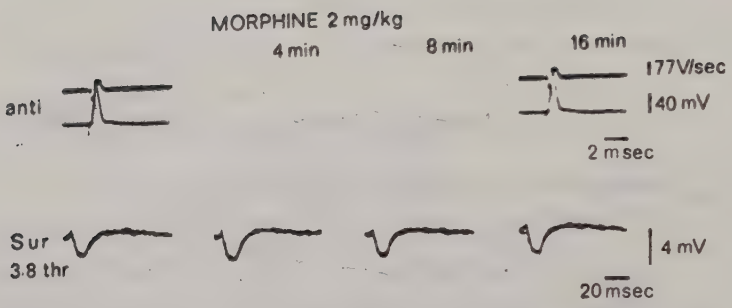


Fig. 4

Effect of morphine on IPSPs elicited in a medial gastrocnemius-soleus motoneurone by stimulation of the sural nerve with single pulses.

3. Interneurone activity.

Depression of polysynaptic EPSPs might have been caused by an inhibition of the impulse discharge from interneurones exerting an excitatory action on the motoneurones. Therefore, the effect of morphine on interneurones located in the neighbourhood of motoneurones in the ventral horn of the spinal cord was tested.

In 6 interneurones, in which the activity was recorded for more than 15 min after the administration of morphine, the drug depressed the repetitive discharge to an activation by single stimulating pulses (Fig. 5 A and B). In 4 of these neurones, it was possible to inject levallorphan 0.2 mg/kg and to test its effect on the action of morphine. Levallorphan always increased the frequency of impulse discharge of the neurones, as is shown by the example of Fig. 5. Here, as in the other 5 interneurones treated with the morphine antagonist, the number of impulses fired after levallorphan was higher than before morphine. Since, however, morphine had already been injected once or twice before starting to record from these interneurones (a period of 60 min at least was interposed between the morphine injection under study and the preceding one), it cannot be decided whether levallorphan exerts an excitatory effect, or whether before the injection of

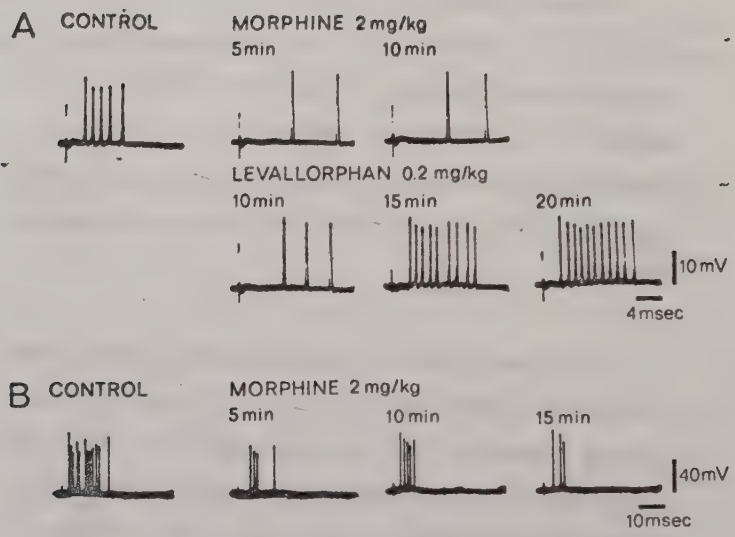


Fig. 5

Effect of morphine and levallorphan on the impulse discharge of two interneurones (A and B) to stimulation of the dorsal root L_7 with single pulses. A: intracellular recording. B: extracellular recording.

morphine, i.e. during the control period, some depressant action had remained from the previous injection.

The inhibitory effect of morphine on interneurones may account for the depression of polysynaptic EPSPs described above. This effect, however, cannot be exerted on spinal interneurones in general, because IPSPs were relatively seldom reduced by morphine. Therefore, an attempt was made to search for spinal interneurones which are not inhibited by morphine in their repetitive discharge to dorsal root stimulation with single pulses. These experiments were performed by gradually moving the micropipettes from the dorsal surface of the spinal cord into the grey matter. The recording depth was read from the micromanipulator. At the end of the experiments, the electrodes were left in the spinal cord, filled with methylene blue, broken about two hours later and the tips searched for under the microscope. The effect of morphine 2 mg/kg was studied in 9 interneurones. In 6 interneurones, which were impaled in a depth between 0.8 - 2.4 mm from the dorsal surface (with reference to the sagittal plane) and identified as interneurones by the duration of the action potentials and the presence of EPSPs, the number of impulse discharges was not reduced by morphine. Three interneurones recorded from at

a greater depth showed a clear reduction in the number of impulse discharges. Before the penetration of these interneurones, field potentials elicited by stimulation of the ventral roots were observed, which was not the case with the 6 neurones mentioned before. It must, therefore, be assumed that these 3 interneurones were located in the neighbourhood of motoneurones.

4. Temporal facilitation of monosynaptic EPSPs.

In a previous study (JURNA, 1966) it had been found that morphine exerts an inhibitory on the reflex discharge from extensor motoneurones when these are activated monosynaptically by a repetitive afferent impulse input from the muscle spindles during muscle stretch. This monosynaptic reflex activation resembles a polysynaptic reflex elicited by a single stimulating pulse applied to the dorsal root in that the motoneurones are activated repeatedly. Repetitive monosynaptic activation may produce temporal facilitation (ECCLES, 1946; LLOYD, 1946) provided that the interval between two subsequent pulses is short enough to allow an EPSPs to add to the depolarization produced by the preceding EPSPs (BROCK et al., 1952). Subliminal EPSPs may thus reach the critical level to generate an action potential and, conversely, reduction of temporal facilitation can prevent a motoneurone from discharging impulses to repetitive activation.

The effect of morphine 2 mg/kg on temporal facilitation was determined in 8 gastrocnemius-soleus motoneurones. In all cases morphine abolished the facilitation produced by trains of pulses applied to the lateral or medial gastrocnemius nerves with a strength just above the threshold of Ia afferents (Fig. 6 A and B). In 3 motoneurones action potentials were set up at random during stimulation after the injection of morphine (Fig. 6 B), although the resting potential had not changed and the facilitated EPSPs did not reach potential values as high as in the controls.

Fig. 6 C presents recordings from a gastrocnemius-soleus motoneurone which was penetrated 12 min after an injection of morphine. Repetitive stimulation of the motor nerve did not produce temporal facilitation of the EPSPs. Facilitation occured, however, for a short period after levallorphan 0.2 mg/kg had been injected. In this case also the EPSPs evoked by the first pulse of the train had increased 5 min after the injection of the drug and diminished together with the reduction of facilitation at 9 min. The resting potential had remained stable throughout the recording time.

5. Excitability changes in primary afferents.

To test whether the depression of temporal facilitation caused by morphine derives from a reduced excitation during repetitive stimulation, excitability changes in primary afferents were determined in four experiments according to the method described by WALL (1958). Orthodromic stimulation of primary afferents with trains of pulses increases the excitability of their terminals. The spike potential evoked by stimulation of the arborizations of the primary afferents and recorded antidromically from the peripheral nerves is increased by a preceding repetitive stimulation of the primary afferents. The magnitude and the time course of the excitability changes are different in the primary afferents from muscles or skin (WALL, 1958).

The results obtained in one experiment each performed on primary afferents from the gastrocnemius-soleus muscles (muscle spindle afferents) and from the skin are presented in Fig. 7. The increase in excitability of the primary afferents of the sural nerve was greater and lasted longer than that of the muscle nerves. Morphine 2 mg/kg abolished the increase in the exitability of the primary afferents from the muscle spindles. In the primary afferents from the skin, only the duration but not the amplitude of the increase in excitability was reduced.

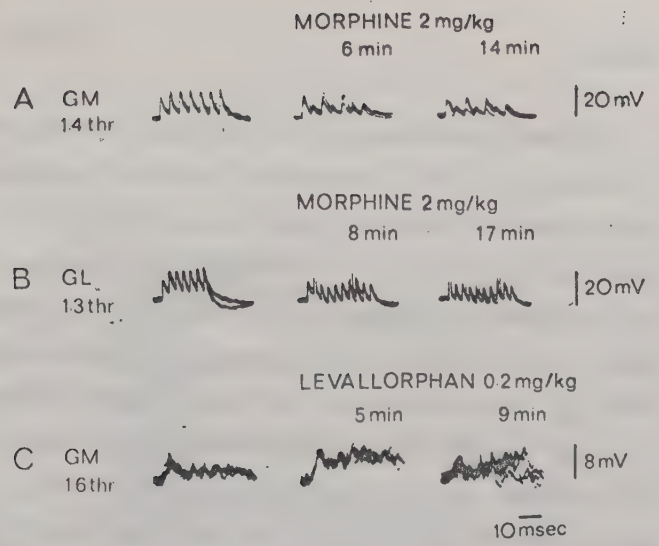


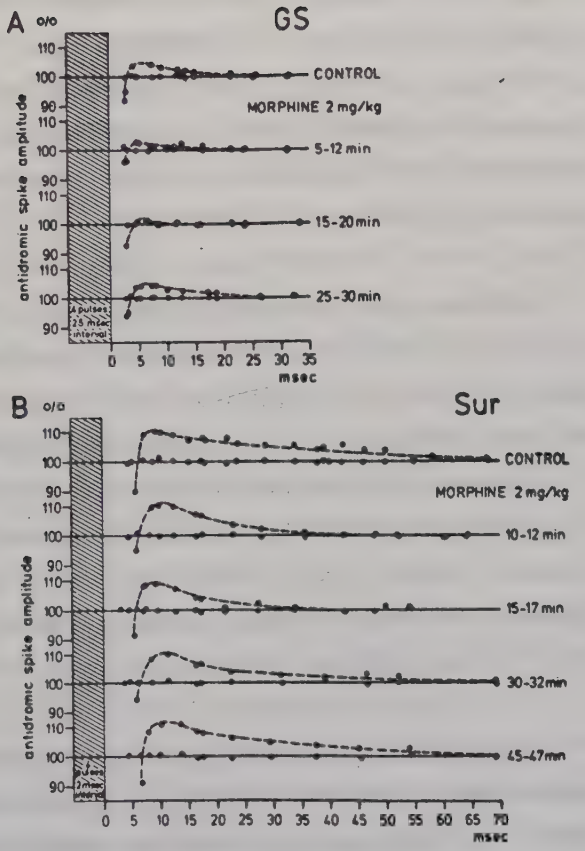
Fig. 6

Effect of morphine and levallorphan on temporal facilitation of monosynaptic EPSPs produced in medial gastrocnemius-soleus (GM) or lateral gastrocnemius (GL) motoneurones by trains of pulses applied to the respective muscle nerves. The stimulation strength in multiples of the threshold is indicated on the left hand of the recordings. The pulse train in A and C consisted of 7 pulses delivered at an interval of 5 msec, and in B of 10 pulses delivered at an interval of 3 msec. In C, the recording made before the administration of levallorphan was obtained from a motoneurone which was penetrated by the microelectrode 12 min after an injection of morphine.

Fig. 7

Effect of morphine on the excitability changes in primary afferent terminals elicited by repetitive stimulation of muscle and skin nerves. The test stimulus was applied to the terminal arborization of the primary afferents in the gastrocnemius-soleus motor nucleus (A) or in the dorsal horn of the spinal cord (B). The response to the stimulus was recorded from the respective peripheral nerve. Conditioning was produced by a train of pulses applied to the medial gastrocnemius (GS) or to the sural nerve (Sur). The ordinates give the changes in the antidromic spike amplitude to the test stimulus in percent of the unconditioned response. The abscissae give the interval between the last pulse of the conditioning train and the test pulse. The hatched areas represent the duration of the conditioning pulse train. Vertical lines and filled circles: amplitudes of the unconditioned responses to the test stimulus. Broken lines and open circles: amplitude of the conditioned response to the test stimuli.

Fig. 7


A
o/o
GS
antidromic spike amplitude
CONTROL
MORPHINE 2 mg/kg
5-12 min
15-20 min
25-30 min
msec
B
o/o
Sur
antidromic spike amplitude
CONTROL
MORPHINE 2 mg/kg
10-12 min
15-17 min
30-32 min
45-47 min
msec

DISCUSSION

The depression of polysynaptic EPSPs caused by morphine may account for the well known inhibition of polysynaptic mass reflexes in spinalized animals. Action potentials evoked by monosynaptic excitation as well as by antidromic stimulation were not influenced by morphine, which is in accord with the observation that monosynaptic mass reflexes are not depressed by low doses of morphine.

Possibly, the depression of polysynaptic EPSPs is due to a reduced impulse discharge from interneurones exerting an excitatory effect on motoneurones. The inhibition of impulse discharges from interneurones does not seem to be a general effect of morphine, because it was observed only in interneurones located in the neighbourhood of motoneurones. However, the number of interneurones tested is too small to draw any final conclusions.

The different sensitivity of interneurones to morphine may be the reason why postsynaptic inhibition evoked from cutaneous afferents was scarcely reduced by the dose of morphine employed. At any rate, polysynaptic EPSPs proved to be much more influenced by morphine than IPSPs. This would be an astonishing result if one assumed that the activity of all spinal interneurones is equally depressed by morphine. A

different action of morphine on different neurones in trigeminal nuclei has been reported by SASA (1969).

The depressant action of morphine on the excitation of motoneurones is not limited to polysynaptic activation, but was also observed during monosynaptic activation of motoneurones with trains of stimuli. The inhibition of temporal facilitation of monosynaptic EPSPs could explain the inhibition of the impulse discharge from alpha motoneurones which were activated from muscle spindle afferents during stretch of extensor muscles (JURNA, 1966). The effect of morphine on temporal facilitation may at least in part be due to the influence of the drug on the excitability of spindle afferent terminals during repetitive stimulation. These terminals were more sensitive to the dose of morphine employed than the terminals of primary afferents from the skin.

From the results presented in this paper and those obtained in previous investigations it is postulated that reflex inhibition produced by morphine is not due to an action of the drug on interneurones, but to an interference with special processes built up by repetitive stimulation in the terminals of afferent fibres converging upon inter- or motoneurones. These processesses may be similar to those responsible for the posttetanic potentiation of monosynaptic reflexes, which is reduced by morphine (JURNA and SCHÄFER, 1965).

SUMMARY - Spinal moto- and interneurones were investigated by means of intra- and extracellular microelectrode recording in spinal cats. Morphine (2 mg/kg) and the morphine antagonist levallorphan (0.2 mg/kg) were injected intravenously. The following results were obtained:

1) The action potentials evoked in motoneurones by ventral root stimulation were not changed in amplitude, duration and rates of rise and fall.

2) Polysynaptic EPSPs elicited in motoneurones by stimulation of the dorsal roots with single pulses were depressed, whereas monosynaptic EPSPs were generally not changed. The depression of polysynaptic EPSPs was antagonized by levallorphan.

3) The IPSPs evoked in gastrocnemius-soleus motoneurones by sural nerve stimulation were scarcely reduced.

4) The repetitive discharge from interneurones located in the neighbourhood of motoneurones was reduced. The reduction of impulse discharges was abolished by levallorphan. The impulse discharge from interneurones situated in dorsal parts of the grey matter of the spinal cord remained unchanged.

5) Temporal facilitation of EPSPs produced in motoneurones by repetitive stimulation of Ia afferents from the gastrocnemius-soleus muscles was depressed. This effect was antagonized by levallorphan.

6) The increase in excitability of the terminals of Ia afferents from the gastrocnemius-soleus muscles produced by repetitive stimulation was depressed. In the terminals of primary afferents of the sural nerve, the increase in excitability was reduced in duration but not in amplitude.

The results obtained are discussed with respect to the inhibition of polysynaptic mass reflexes in spinalized animals, and it is suggested that morphine may influence processes which are generated by repetitive activation.

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und die Überlassung dieses Themas für meine
Doktorarbeit.

Homburg, den 2. November 1972

Dr. Werner G r o s s m a n n

L e b e n s l a u f

Ich, Dr. Werner Grossmann, wurde am 11. Juli 1940 als Sohn von Herrn Dr. Kurt und Dr. Elisabeth Grossmann in Wien geboren.

Nach der Grundschule absolvierte ich das humanistische Gymnasium im Stift Melk (Österreich), wo ich 1959 die Matura mit Erfolg ablegte. Im WS 1959/60 immatrikulierte ich an der Medizinischen Fakultät der Universität Wien, erlangte das Absolutorium im WS 1965/66 und promovierte im SS 1967. Während meines Studiums war ich als Demonstrater bzw. als wissenschaftliche Hilfskraft 2 Jahre am Anatomischen Institut und 1 Jahr am Pathologischen Institut der Universität Wien, sowie ein halbes Jahr am Pharmakologischen Institut der Ruhr-Universität Bochum tätig. Am 1. September 1967 trat ich als wissenschaftlicher Assistent in das Pharmakologische Institut der Ruhr-Universität Bochum ein. Zum Erlernen pharmazeutischer Screeningmethoden besuchte ich 4 Monate die pharmazeutische Firma BYK-Gulden Lomberg, Konstanz. Im folgenden Jahr arbeitete ich mit Prof. Dr. Kraupp (Pharmakologisches Institut der Ruhr-Universität Bochum) am Wirkungsmechanismus von coronarwirksamen Substanzen. Meine neuropharmakologische Tätigkeit begann 1969 mit Untersuchungen am Limbischen System zusammen mit Prof. Dr. Brust-Carmona (Mexico City) und Prof. Dr. Stumpf (Wien). Seit Anfang des Jahres 1970 bin ich als Gastassistent am Pharmakologischen Institut in Homburg und arbeite im Rahmen des Sonderforschungsbereiches 38 "Membranen" zusammen mit Prof. Dr. Jurna in der Gruppe "Neuropharmakologie".

Infolge der gesetzlichen Neuregelung der Ausbildung zum Facharzt für Pharmakologie habe ich im Frühjahr 1972 das deutsche Staatsexamen für Medizin an der hiesigen Medizinischen Fakultät absolviert.

Dr. Werner Grossmann